Systemic sclerosis – a microvascular disorder?[1]

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Introduction

Systemic sclerosis (SS) is a multisystem disorder characterized by a variable combination of connective tissue and particularly collagen proliferation, mild chronic inflammatory cell infiltration, vascular obstruction and ischaemic atrophy. These features occur to differing extents in various organ systems and lead to the clinical and pathological changes of the disease. Although there are a number of different subtypes such as the CREST syndrome, acrosclerosis, and diffuse forms, they have many overlapping features and frequently it is difficult to classify individual cases definitively into particular subgroups. Most commonly the disease presents with Raynaud's phenomenon and is followed by progressive induration and stiffening of the skin, particularly peripherally, with variable involvement of the joints, oesophagus, small bowel, large bowel, heart, lungs and kidneys.

Vascular changes

Raynaud's phenomenon is a syndrome of reversible peripheral ischaemia which occurs predominantly in the hands but also in the feet. It is usually precipitated by cold and sometimes by emotion or other poorly recognized events. The fingers turn white and then become cyanosed, and during the warming phase they may turn bright red due to profound vasodilatation. Pain with numbness and paraesthaesiae is common. Analogous changes in blood flow have been observed in the kidneys (Cannon *et al.* 1974), the lungs (Furst *et al.* 1981) possibly accounting for a corresponding seasonal change in diffusing capacity (Emmanuel *et al.* 1976), and the heart (Alexander *et al.* 1981). More severe and persistent peripheral ischaemia of the fingers may lead to small areas of infarction at the finger tips and elsewhere. Most common are ulcerations which heal to give the appearance of pitting and atrophy of the pulps of the finger tips. There is a risk of secondary infection, and recurrent infections may eventually lead to auto or surgical amputations.

Careful examination of the skin will show dilated capillaries. These telangiectasiae are particularly prominent on the face and on the palms of the hands but also occur elsewhere. The nail beds may appear swollen and by the technique of capillary microscopy (Maricq 1981) it is possible to see a specific pattern of enlarged and deformed capillary loops surrounded by avascular areas (Maricq *et al.* 1980). This pattern will distinguish between patients with primary Raynaud's disease and those with Raynaud's phenomenon due to SS (Maricq *et al.* 1982). The extent of capillary change shows some correlation with visceral disease (Maricq *et al.* 1976).

There is a number of excellent studies on the pathology of the vascular changes in SS (Norton & Nardo 1970, Cannon *et al.* 1974, Campbell & LeRoy 1975). In general, the frequency of vascular abnormalities is inversely proportional to the size of the blood vessels. Involvement of the large and medium-sized arteries is rare but has been recorded (Furey *et al.* 1975), whereas lesions are common in the small arteries and arterioles. In the arterioles (50–150 μ) the principal changes are of intimal sclerosis with fibrinoid change and necrosis.

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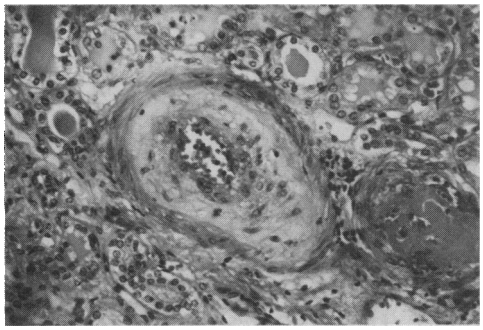

Figure 1. Renal arteriole in systemic sclerosis showing marked intimal thickening

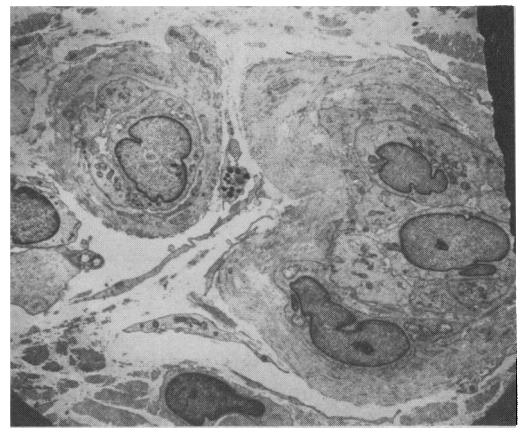

Figure 2. Systemic sclerosis capillaries showing grossly thickened basement membranes (× 5000)

In the small arteries (150–500 μ) there is marked intimal thickening due to proliferation and swelling of endothelial cells, and deposition of a mucoid ground substance with fine collagen fibrils (Figure 1) together with fibrinogen or fibrin deposits (Fennel *et al.* 1961). Around the adventitia is a cuff of fibrous tissue and there may be an infiltration of mononuclear cells. In advanced disease the lumen of the vessel may be completely obstructed but later recanalization can occur. Eventually the specific features may be replaced by blood vessel fibrosis and atrophy.

There is a marked reduction in the number of capillaries to perhaps only 20% of the normal with profound devascularization of the tissues. The remaining capillaries are dilated and may show extreme capillary wall thickening with thickening of the basement membrane (Figure 2) and endothelial cell swelling.

These pathological features are widespread and are frequently found in the absence of frank clinical involvement (D'Angelo *et al.* 1969). In the fingers, obstruction of the digital arteries can be detected by arteriography (Dabich *et al.* 1972) but there is a poor correlation between the severity of the vascular disease and the sclerodermatous change in the skin. Although this raises some doubt about whether ischaemia can be regarded as the cause of the excessive fibrosis, it does not exclude microvascular disease as this does not necessarily correlate with the larger digital artery involvement.

In the presence of widespread and profound disease affecting the small arteries, arterioles and capillaries, it is reasonable to consider whether SS is fundamentally a microvascular disorder; the mechanisms of the microvascular changes; whether it is possible to treat or control these mechanisms; and if successful treatment of the microvascular disease will affect the progress of the fibrosis.

Physiology and measurement of the microcirculation

The capillaries are the smallest vessels in the circulation. The arterioles empty into the capillaries which in turn empty into venules. The arterioles and venules are also connected by short-circuiting vessels which bypass the capillaries. The passage of blood through these shunts and through the capillaries is controlled by smooth muscle cells forming pre-capillary sphincters.

Only the capillary blood has a nutritional function. In the skin a series of superficial loops form a nutritional network and the shunting system lies in the deeper layers. Opening of this shunting system will deprive the more superficial tissues of an adequate blood supply. The shunted blood flow is the principal source of heat and thermoregulatory system for the skin. It is possible for all blood to be shunted through the deeper layers so that the skin remains warm yet may become gangrenous (Fagrell 1977). Recent technological advances allow

measurement of various components of the blood flow in the skin, and these provide a basis for understanding the physiological changes in SS and for assessing the results of various forms of treatment. The laser light-scattering method depends on analysis of the frequency spectrum of laser light scattered by moving red cells in the skin (Gush *et al.* 1982) and seems to be the most useful at the present time.

Measurements of the peripheral microcirculation in the skin of SS patients confirm the reduction of nutritional flow with an excessive further reduction on exposure to cold (Coffman & Cohen 1971, LeRoy *et al.* 1971, Haavik Nilsen & Jayson 1980).

Mechanisms of microvascular damage in systemic sclerosis

Sympathetic system

Sympathetic over-activity could cause profound vasoconstriction and peripheral ischaemia. However the evidence for this is weak. Peacock (1959) found elevated levels of circulating catecholamines but this was not confirmed by Sapira *et al.* (1972). Winkelmann *et al.* (1977) showed that isolated peripheral vessels from SS patients lost their reactivity to catecholamines more rapidly than controls at low temperatures with delayed reacquisition of reactivity on rewarming, but it is difficult to be sure whether this is a specific change or merely a feature of damaged vessels. Measurements of electrical skin resistance have shown no evidence of sympathetic hyperactivity (Fries 1969) and histological examination shows destruction of the nerve network (Pawlowski 1963) which tends to suggest decreased sympathetic activity. Although sympathectomy may produce some transient improvement it does not influence the long-term course of the disease (Johnston *et al.* 1965). Both oral (Coffman & Cohen 1971) and intra-arterial (Haavik Nilsen & Jayson 1980) reserpine can improve the peripheral circulation in SS. Reserpine is thought to act by depleting the peripheral nerve endings of noradrenaline, but the prolonged remissions that may occur after a single injection suggest that some other mechanism may be operating.

Serotonin (5-hydroxytryptamine, 5-HT) metabolism

Serotonin, first recognized as a serum blood pressure raising agent, is formed in the enterochromaffin cells of the gastrointestinal tract and is stored and released by the circulating platelets. Its principal actions are to cause vasoconstriction and initiate and amplify platelet adhesion and aggregation.

Subcutaneous injection of 5-HT in experimental animals produces skin changes remarkably similar to those of SS (MacDonald *et al.* 1958), and *in vitro* studies show that serotonin can stimulate fibroblast growth (Boucek & Noble 1973) and increase collagen synthesis (Boucek *et al.* 1972). Infusion of 5-HT into the pulmonary arteries of experimental animals produces pathological changes of pulmonary hypertension typical of SS (Rossi & Zamboni 1958), and when infused into the brachial arteries of man 5-HT produces the features of Raynaud's phenomenon (Roddie *et al.* 1955). Scleroderma-like lesions have been reported in association with carcinoid tumours (Fries *et al.* 1973) and during treatment with L-5 hydroxytryptophan and carbidopa (Sternberg *et al.* 1980) which is thought to lead to high serotonin and kynurenine levels. Isolated strips of vascular smooth muscle from SS patients are hypersensitive to serotonin compared with specimens from control subjects (Winkelmann *et al.* 1976).

However, 5-HIAA, which is the principal metabolite of serotonin, is excreted in normal or reduced amounts in the urine (Tuffanelli 1963). This observation cast doubt on the role of serotonin until Stachow *et al.* (1977) demonstrated that although the resting 5-HIAA excretion is normal in SS there is lack of the normal increase after oral loading with l-tryptophan, suggesting impaired transformation of serotonin to 5-HIAA due to diminished activity of monoamine oxidase. This would lead to elevated serotonin levels in the presence of normal or reduced 5-HIAA excretion. Measurements of biogenic amines derived from tryptophan (Stachow *et al.* 1979) suggest reduced levels of monoamine oxidase and some correlation between elevated 5-HT levels and the severity of the disease. Inhibitors of monoamine oxidase may cause Raynaud's phenomenon (Halpern *et al.* 1960, Hines 1955).

Tomlinson & Jayson (in preparation) recently found a possible association between SS and treatment with appetite suppressants. These drugs may control appetite, producing the sensation of satiety by serotoninergic mechanisms.

In contrast, however, the uptake and levels of serotonin in platelets from SS patients were reported as normal (Adelson *et al.* 1982). However these were limited studies in patients with long-standing disease.

Interest in the role of 5-HT led to consideration of the use of specific antagonists in the management of SS and Raynaud's phenomenon. Early studies of a nonspecific 5-HT antagonist (Halpern *et al.* 1960) suggested some benefit. More recently two distinct tissue serotonin receptors have been recognized and the specific 5-HT_2 antagonist, Ketanserin, developed. Recently we have studied the acute effects of this agent given intravenously to patients with SS and Raynaud's phenomenon and found a dramatic increase in the peripheral microcirculation. These benefits were transient but were so marked that they have encouraged us to conduct a long-term controlled trial using an oral preparation.

Endothelial damage and platelet activation

The initial lesion may well lie in the endothelial cells, with some form of damage leading to increased permeability and the subsequent development of fibrosis. Pathological examination of the arterioles and capillaries shows striking intimal hyperplasia and endothelial cell damage (Figure 1) with basement membrane thickening (Figure 2) and reduplication, and fibrin-like material in the vessel wall (Norton 1970). Autoradiography shows a marked increase of labelling of endothelial and periendothelial cells (Fleischmajer *et al.* 1976). Evidence of endothelial damage has been demonstrated in SS by the presence of increased circulating Factor VIII/von Willebrand factor antigen and von Willebrand factor activity (Kahaleh *et al.* 1981). Elevated levels of circulating platelet aggregates and β-thromboglobulin (Kahaleh *et al.* 1982) indicate activation of platelets and it is known that β-thromboglobulin diminishes prostacyclin production (Hope *et al.* 1979). Platelet adherence to the endothelium occurs more readily in steady than in pulsatile flow (Sakariassen *et al.* 1980) and therefore would be more likely to occur in the peripheral microcirculation (Caro *et al.* 1978). The possible role of platelet activation in the microvascular lesion led Kahaleh *et al.* (1982) to use antiplatelet therapy (low-dose aspirin plus dipyridamole) in the management of SS. They were able to correct the evidence for platelet activation but it is not yet known whether this has any effect on the outcome of the disease.

Kahaleh *et al.* (1979) produced evidence for a circulating endothelial cell cytotoxic factor which could be the cause of the endothelial cell damage. However in very detailed studies we have not been able to confirm this finding (Summers *et al.* 1983) despite using a system sensitive to other known cytotoxic agents.

Prostaglandins E_1 and I_2 are effective agents in antagonizing the effects of thromboxane and interfering with platelet aggregation, and will improve peripheral blood flow (Dowd *et al.* 1981, Martin & Tooke 1982). Current work is directed at studying a new thromboxane synthetase inhibitor to determine its effects on the microcirculation and disease parameters.

Blood hyperviscosity

Increased viscosity of the blood occurs in SS (Goyle & Dormandy 1976, McGrath *et al.* 1977), particularly at low shear rates and low temperatures as in the periphery, and may be due to reduced red cell deformability or to elevated fibrinogen levels. Infusions of prostaglandins I_2 and E_1 improve the microcirculation and one mechanism may be an improvement in red cell deformability (Dowd *et al.* 1981). Plasmapheresis has been used to reduce the blood fibrinogen levels (O'Reilly *et al.* 1979) but also may improve red cell deformability (Dodds *et al.* 1979).

Fibrin metabolism in systemic sclerosis

Elevated fibrinogen levels in the blood may contribute towards peripheral ischaemia not only by increased plasma viscosity but also because fibrin deposits on the vessel walls,

usually associated with platelet adherence, lead to progressive lumen narrowing. Elevated fibrinogen levels are the result of impaired fibrinolytic activity (Cunliffe & Menon 1969, Jarrett *et al.* 1978) and in many cases defective plasminogen activator release from vascular endothelium (Holland & Jayson 1983). In particular, this may be responsible for poor clearance of fibrin deposits in the walls of small blood vessels (Fennell *et al.* 1961). Microangiopathic haemolytic anaemia may result from fragmentation of red cells due to contact with intravascular fibrin (Salyer *et al.* 1973). Infusions of low molecular weight dextran will correct the fibrinolytic abnormalities (Cunliffe & Menon 1969) and improve the peripheral microcirculation (Tomlinson *et al.* 1983).

These observations led to studies of fibrinolytic enhancement therapy using the non-virilizing androgenic steroid stanozolol. Preliminary results (Jarrett *et al.* 1978) suggest that this treatment is of value not only in improving the fibrinolytic parameters but also the peripheral blood flow. They did not detect any influence on other parameters of SS except for grip strength but this could have been due to the androgenic properties of the drug. We are currently conducting a more detailed long-term study of stanozolol therapy.

Of great relevance is a non-connective tissue disorder, liposclerosis of the leg, which may follow venous thrombosis with chronic induration and fibrosis. Extravascular fibrin deposition occurs and is associated with diminished fibrinolysis and correlates with the extent of fibrosis and inflammation (Burnand *et al.* 1982). Fibrinolytic enhancement therapy with stanozolol significantly improves the clinical evidence of fibrosis and inflammation as well as the fibrinolytic parameters (Browse *et al.* 1977).

Immunological factors

Although many patients with SS may show overlap features with other connective tissue diseases (Sharp *et al.* 1972) there is little evidence that serological factors such as immune complexes play a direct role in the pathogenesis of the vascular lesions. Complement-fixing serological factors may react with the blood vessel walls (Tan & Pearson 1972), and immune complex deposition has been demonstrated in the intimal lesions of small arteries within the kidney (Lapenas *et al.* 1978). However, circulating immune complexes have been found to varying extents (Seibold *et al.* 1982, Siminovitch *et al.* 1982) and a mixed cryoglobulinaemia is often present (Husson *et al.* 1976), but they do not show much correlation with the clinical features. In the early stages of the disease there may be a perivascular cuff of chronic inflammatory cells around the small arteries which is progressively obliterated with advancing fibrosis and atrophy (Campbell & LeRoy 1975). This perivascular accumulation of chronic inflammatory cells could be a response to specific immunological events or a feature of chronic vascular damage. It is possible that lymphokines derived from stimulation of human mononuclear cells act as the stimulus to fibroblasts to secrete excess collagen (Johnson & Ziff 1976).

Is there a microvascular basis for fibrosis in systemic sclerosis?

Fibrosis and microvascular disease are the hallmarks of SS. It is uncertain whether the two occur simultaneously or whether one is the consequence of the other. There is a certain amount of evidence to suggest that microvascular disease is the primary pathogenetic disorder and provides the basis for the proliferation of connective tissue and particularly collagen in SS.

There are a number of anecdotal reports of control of scleroderma renal crises causing regression of both the cutaneous features of the disease and the Raynaud's phenomenon (Wasner *et al.* 1978, Whitman *et al.* 1982). The evidence that serotonin can stimulate collagen synthesis has already been reviewed and it is known that other platelet-derived factors can activate myofibroblasts (Castor *et al.* 1979). Tissue disruption may be associated with the release of vasoactive substances that stimulate collagen synthesis. Immunofluorescent examination of skin biopsies shows the proliferation of A and B collagen chains typical of vessel wall collagen (Gay *et al.* 1980). The presence of circulating antibodies to types I and IV collagen (Mackel *et al.* 1982) suggest that vascular collagen

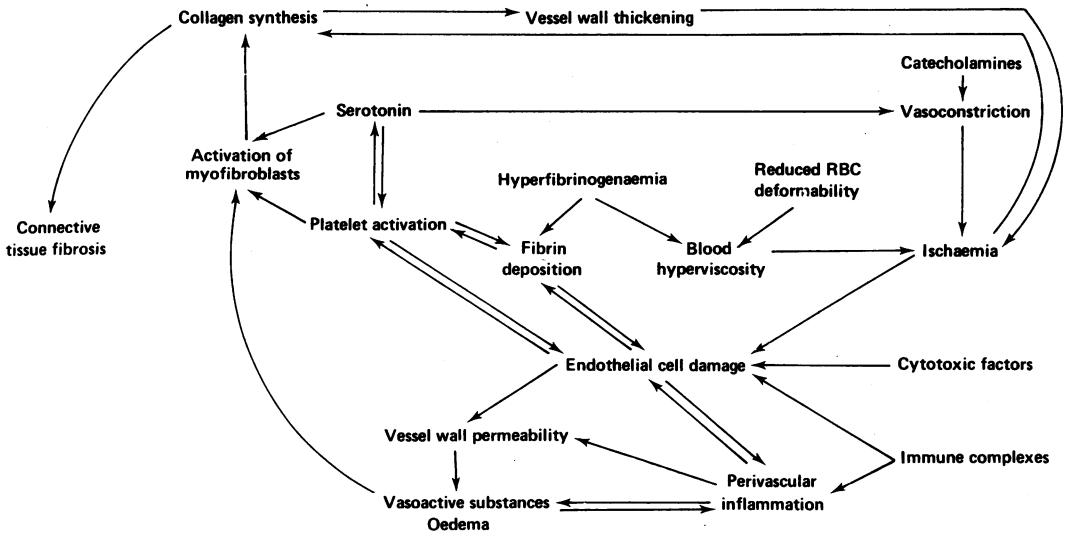

Figure 3. Possible microvascular mechanisms involved in the pathogenesis of systemic sclerosis

does play a fundamental role in this disease in that type IV collagen is characteristic of blood vessel walls.

It is possible that ischaemia itself is responsible for excess collagen synthesis and is the mechanism of scar formation during wound healing. Chvapil *et al.* (1973) showed that a decrease in oxygen supply to a tissue prevents the aerobic metabolism of glucose and results in excessive production of lactic acid. Lactic acid has been shown to activate propyl hydroxylase and so could stimulate collagen synthesis.

An important analogy is the observation that 30% of children with insulin-dependent diabetes mellitus develop thickening and induration of the skin of the fingers and many have mild flexion contractures, the clinical pattern resembling SS (Seibold 1982). There is an association with the microvascular complications of diabetes (Rosenbloom *et al.* 1981) which in turn are associated with increased capillary permeability. These observations lend support to the concept that microvascular disease may underlie the fibrotic features of SS.

Conclusions

Microvascular disease forms a fundamental part of SS and may be responsible not only for the vascular problems such as Raynaud's phenomenon, ischaemia and ischaemic atrophy, but also for the general fibrosis. Figure 3 illustrates a hypothesis of the microvascular basis of this disorder. A number of different underlying mechanisms have been identified and may be amenable to therapeutic intervention particularly if initiated early. Current work is directed at determining the most effective ways of treating the microvascular problems and examining their effects on the prognosis of the disease.

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